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Abstracts

Speaker Abstracts for the 2nd International Meeting on Molecular Staging of Cancer, 22–26 June 2006, Heidelberg, Germany

S1. CELL SIGNALING BY RECEPTOR TYROSINE KINASES: FROM BASIC CONCEPTS TO CLINICAL APPLICATIONS

Joseph Schlessinger. *Yale University School of Medicine, Department of Pharmacology, P.O. Box 208066 New Haven, CT 06520, USA.*

Receptor tyrosine kinases (RTKs) comprise a large family of cell surface receptors that control many critical cellular processes. The intrinsic protein kinase activity of RTKs is stimulated following growth factor binding to the extracellular ligand-binding domain which stimulates receptor dimerization, tyrosine autophosphorylation and enhancement of enzymatic activity leading to the recruitment and activation of multiple intracellular signaling pathways. It is now well established that various human diseases and pathologies are caused by dysfunction in RTKs or in the intracellular signaling pathways that they activate. These include many cancers, developmental abnormalities, sever bone disorders, immune diseases, arteriosclerosis and angiogenesis among others.

We have used mass spectrometry and X-ray crystallography to demonstrate that tyrosine autophosphorylation of the catalytic tyrosine kinase domain of FGF-receptor-1 (FGFR1) is mediated by a sequential and precisely ordered reaction. We also demonstrate that the rate of catalysis of two FGFR substrates is enhanced by 50–100-fold following autophosphorylation of the first site in the activation loop while autophosphorylation of the second site in the activation loop results in 500–1000-fold increase in the rate of substrate phosphorylation. We propose that FGFR1 is activated by a two-step mechanism mediated by strictly ordered and regulated autophosphorylation suggesting that distinct phosphorylation states may provide both temporal and spatial resolution to receptor signaling. Genetic models in mice provide new opportunities for exploring and developing new treatments for diseases caused by dysfunctions in RTKs and in their intracellular signaling pathways. Inhibitors of tyrosine kinases have been successfully applied for the treatment of cancers driven by activated tyrosine kinases. Sutent/SU11248 is a new drug that blocks the actions of several tyrosine kinases including c-Kit, PDGFR and VEGFR. Sutent has been approved by the FDA for the treatment of gastrointestinal stromal tumors (GIST), Gleevec resistant GIST, advanced kidney cancers as well as other cancers. The approval marks the first time the FDA has approved a new oncology product for two indications simultaneously. Finally, a novel scaffold-based drug discovery approach will be described that enables the development of many new families of inhibitors for protein kinases and other enzymes that play a role in cell signaling.

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S2. Src-FROM ONCOGENE TO CLINICAL TARGET

Justin M. Summy, Michael J. Gray, Gary E. Gallick. *Department of Cancer Biology, University of Texas, M.D. Anderson Cancer Center, TX, United States.*

The protein tyrosine kinase, Src, is the founding member of a nine-gene family that regulates such diverse processes as proliferation, migration, invasion, cell survival and angiogenesis. Aberrantly high Src activity is seen in numerous human tumors, with increases in Src activity associated with progressive stages of disease and poor prognosis. In mouse models for several types of human tumors, we demonstrate that Src activation increases metastatic potential with limited effects on primary tumor growth. In these models, pharmacologic inhibitors of Src retard growth of large tumors and inhibit the development of metastases. Therefore, small molecule Src-selective inhibitors are now in clinical trial in advanced stages of a number of solid tumors. However, given its diverse modifications, Src itself may not represent the best marker for effectiveness of these therapeutic agents. Therefore, we have examined Src signaling pathways that promote tumor progression, with an emphasis on pro-angiogenic pathways. Src regulates expression of vascular endothelial growth factor (VEGF) by activating Akt, p38 and STAT3. In addition, Src regulates IL-8 expression in a pathway requiring

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